Feasibility of, and critical paths for mycophenolate mofetil Bayesian dose adjustment: Pharmacological re-appraisal of a concentration-controlled versus fixed-dose trial in renal transplant recipients

Titre	Feasibility of, and critical paths for mycophenolate mofetil Bayesian dose adjustment: Pharmacological re-appraisal of a concentration-controlled versus fixed-dose trial in renal transplant recipients
Type de publication	Article de revue
Auteur	Prémaud, Aurelie [1], Rousseau, Annick [2], Le Meur, Yannick [3], Venisse, Nicolas [4], Loichot-Roselmac, Cecile [5], Turcant, Alain [6], Hoizey, Guillaume [7], Compagnon, Patricia [8], Hary, L. [9], Debruyne, Danièle [10], Saivin, S. [11], Jacqz-Aigrain, E. [12], Marquet, Pierre [13]
Editeur	Elsevier
Type	Article scientifique dans une revue à comité de lecture
Année	2010
Langue	Anglais
Date	2010/02
Numéro	2
Pagination	167 - 174
Volume	61
Titre de la revue	Pharmacological Research
ISSN	1043-6618
Mots-clés	Bayesian dose adjustment [14], Concentration-controlled versus fixed-dose trial [15], Mycophenolate mofetil [16], Renal transplantation [17]

Résumé en anglais	The aim of this study was to analyze retrospectively and critically the different steps of the individual dose adjustment procedure employed in the concentration-controlled (CC) versus fixed-dose trial Apomygre, which showed that mycophenolate mofetil (MMF) dose adjustment using a limited sampling strategy significantly reduced the risk of treatment failures and acute rejection in renal transplants at one year posttransplantation.The number of AUCs performed during the study and circumstances of collection, time of blood sampling, Bayesian mycophenolic acid (MPA) area-under-the-curve (AUC) estimation procedures and physicians' compliance with MMF dose recommendations were retrospectively analyzed. 92% of AUCs scheduled over the study were actually performed. Sampling times were very well respected. Bayesian estimation of MPA exposure was done by the pharmacologists locally in accordance with the protocol instructions and the AUC estimates obtained were virtually all confirmed a posteriori. On the other hand, a second AUC estimated by multiple linear regression could only be provided for 84% of the profiles and showed a large overestimation with respect to Bayesian estimates for AUC values between 10 and 55 mg h/L. In the CC arm, a very good physicians' compliance was observed (85%) and application of the dose recommendations led to higher values of AUCs (42.1 ± 14.6 mg h/L versus 36.7 ± 16.3 mg h/L, p = 0.0035) and to more AUCs in the target range (69% versus 56%, p = 0.0343) than when dose recommendations were not applied. By analyzing in detail the feasibility criteria of MMF Bayesian dose adjustment, this study highlighted the requirements for successful extrapolation of the Apomygre trial results to routine practice: (i) respect of the PK sampling time-windows; (ii) use of relevant tools for accurate drug exposure estimation and dose adjustment calculation; and (iii) good compliance of the physicians with regard to the recommended doses.
URL de la notice	http://okina.univ-angers.fr/publications/ua4957 [18]
DOI	10.1016/j.phrs.2009.09.006 [19]
Lien vers le document	http://dx.doi.org/10.1016/j.phrs.2009.09.006 [19]

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[19] http://dx.doi.org/10.1016/j.phrs.2009.09.006